

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C. 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 12 September 2000 (12.09.00)	
International application No. PCT/US00/02026	Applicant's or agent's file reference 5452-PCT
International filing date (day/month/year) 26 January 2000 (26.01.00)	Priority date (day/month/year) 26 January 1999 (26.01.99)
Applicant SKIBO, Edward, B.	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
26 June 2000 (26.06.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

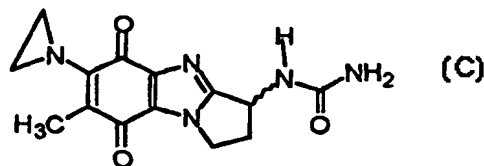
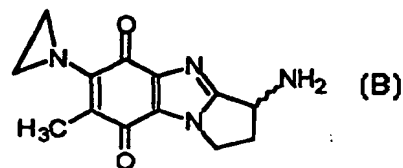
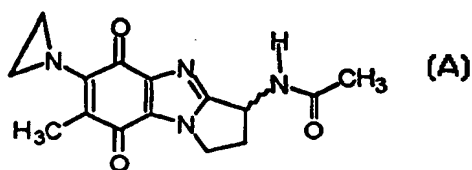
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Charlotte ENGER Telephone No.: (41-22) 338.83.38
--	--



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/415	A1	(11) International Publication Number: WO 00/43005 (43) International Publication Date: 27 July 2000 (27.07.00)
<p>(21) International Application Number: PCT/US00/02026</p> <p>(22) International Filing Date: 26 January 2000 (26.01.00)</p> <p>(30) Priority Data: 60/117,199 26 January 1999 (26.01.99) US</p> <p>(71) Applicant (for all designated States except US): ARIZONA BOARD OF REGENTS, a body corporate of THE STATE OF ARIZONA, acting for and on behalf of ARIZONA STATE UNIVERSITY [US/US]; Tempe, AZ 85287 (US).</p> <p>(72) Inventor; and (75) Inventor/Applicant (for US only): SKIBO, Edward, B. [US/US]; 5711 East Edgemont Drive, Scottsdale, AZ 85257 (US).</p> <p>(74) Agent: MYBECK, Richard, R.; Suite 10, 8010 East Morgan Trail, Scottsdale, AZ 85258 (US).</p>		<p>(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published With international search report.</p>

(54) Title: TREATMENT OF NEOPLASMS WITH THE YUJUNGAMYCINS



(57) Abstract

Pyrrolo[1,2- α]benzimidazoles having structural formulae (A), (B) and (C) were prepared as reductive alkylating agents of DNA. In these compounds only the reduced (hydroquinone) form acts as the alkylating agent. DT-diaphorase is the prerequisite two-electron reducing enzyme which carries out the activation process. Depending on the cancer cell line organ and species source, the substrate and inhibition properties of the enzyme can vary widely. Therefore the design of the yujungamycins was to take advantage of subtle differences in the enzyme structure among cancer cell lines. In doing so, cancer-cell-selective drugs were designed possessing outstanding *in vivo* activity. The 3-substituent influences the reductive activation process and the substituents (amino, acetamido, and carbamido) were placed at this position with varying configuration (R and S). The variation in hydrogen bonding and stereochemistry permits the yujungamycins to recognize DT-diaphorase from select cancer cells resulting in a "magic bullet" directed toward such cells.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/02026

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/415

US CL :514/394

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/394

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
noneElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE: yujungamycin or yjugamycin, ?aziridinyl?, ?benzimidazol?, ?pyrrol? with cancer or neoplas?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,246,955 A (SKIBO et al) 21 September 1993.	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

07 MARCH 2000

Date of mailing of the international search report

06 APR 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

KIMBERLY JORDAN

Telephone No. (703) 308-1235

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 24 AUG 2000

WIPO


Applicant's or agent's file reference 5452-PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/02026	International filing date (day/month/year) 26 JANUARY 2000	Priority date (day/month/year) 26 JANUARY 1999
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 31/415 and US Cl.: 514/394		
Applicant ARIZONA BOARD OF REGENTS, A BODY CORPORATE OF THE STATE OF ARIZONA, ACTING FOR AND ON BEHALF OF ARIZONA STATE UNIVERSITY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 3 sheets.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 26 JUNE 2000	Date of completion of this report 08 AUGUST 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  KIMBERLY JORDAN
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/02026

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☒ the description:

pages 1-28, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

☒ the claims:

pages 28-30, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

☒ the drawings:

pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

☒ the sequence listing part of the description:

pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
- ☒ the claims, Nos. NONE
- ☒ the drawings, sheets/fig NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/02026

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)	Claims <u>1-10</u>	YES
	Claims <u>none</u>	NO
Inventive Step (IS)	Claims <u>1-10</u>	YES
	Claims <u>none</u>	NO
Industrial Applicability (IA)	Claims <u>1-10</u>	YES
	Claims <u>none</u>	NO

2. citations and explanations (Rule 70.7)

Claims 1-10 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest compositions or methods of treating neoplastic diseases with yujungamycins. The methods and compositions would be useful in the oncology field.

----- NEW CITATIONS -----

NONE